A Catalytic Asymmetric Synthesis of α-Methylene Lactones by the Palladium-catalysed Carbonylation of Prochiral Alkenyl Halides

Takeyuki Suzuki, Yasuhiro Uozumi and Masakatsu Shibasaki*

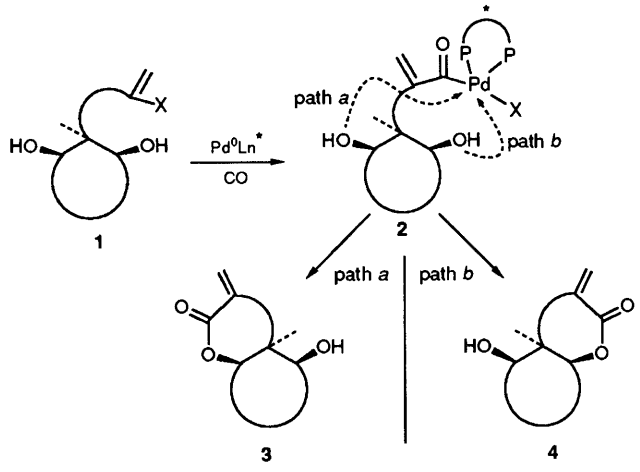
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

A catalytic asymmetric synthesis of the α-methylene lactones starting with the prochiral alkenyl halides **8** and **19** has been achieved for the first time, giving **9** in 57% enantiomeric excess (e.e.) and **20** in 39% e.e., respectively.

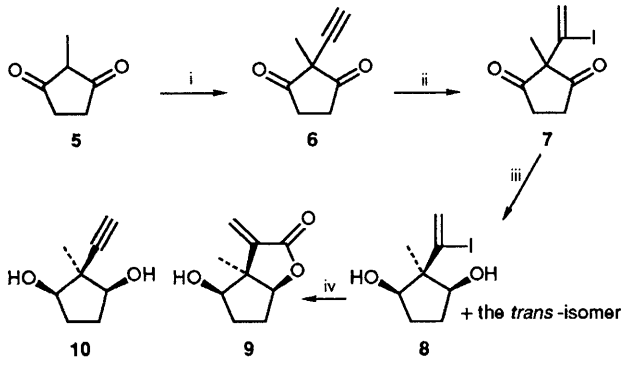
Metal complex catalysed carbonylation reactions offer useful methods for the syntheses of carboxylic acids, esters, amides, aldehydes *etc.*, and these methods are of considerable industrial value. However, application of a carbonylation reaction to a catalytic asymmetric synthesis is rather difficult owing to the fact that carbon monoxide is capable of functioning as a ligand to a transition metal. Thus, a catalytic asymmetric synthesis using carbon monoxide and a transition metal is one of the most challenging research fields in synthetic organic chemistry. To date successful results in catalytic asymmetric hydroformylation of alkenes,[1,2] hydroesterification[1,3] and hydrocarboxylation[4] have been reported. However, no successful carbonylation in a catalytic asymmetric synthesis starting with alkenyl halides has been reported.[5] In this communciation we report the first example of a catalytic asymmetric synthesis of the α-methylene lactones **9**, **13** and **20** starting from the prochiral alkenyl halides **8** and **19**.

We have already achieved several enantiotopic group selective ring closures of prochiral alkenyl halides by an asymmetric Heck reaction, giving bicyclic molecules of high e.e.[6] It was envisioned that application of the same concept to carbonylation of the prochiral alkenyl halide with an internal hydroxy group **1**, which possesses a *meso* plane of symmetry, would produce the optically active α-methylene lactone **3** or **4**. That is, oxidative addition of **1** to Pd^0 with an optically active bidentate phosphorus ligand, followed by insertion of carbon monoxide into the resulting metal–carbon bond, would give the palladium acyl complex **2**, which would differentiate the two hydroxy groups to afford the α-methylene lactone **3** or **4** in an optically active form.

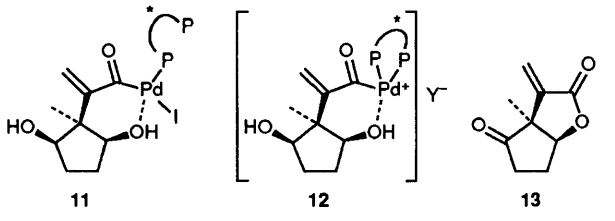
First of all, a catalytic asymmetric synthesis of the α-methylene-γ-butyrolactone **9**, which would find immediate application in the synthesis of pharmacologically exciting molecules,[7] was undertaken. The requisite prochiral alkenyl iodide **8** was effectively synthesized as follows. Treatment of the diketone **5** with potassium *tert*-butoxide in *tert*-butyl alcohol (30 °C, 1 h) followed by addition of ethynyl(phenyl)iodonium tetrafluoroborate (30 °C, 2 h) afforded the acetylenic diketone **6** in 55%



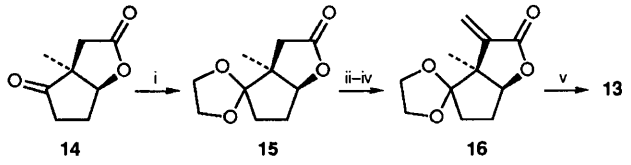
Scheme 1



Scheme 2 *Reagents and conditions*: i, Bu^{t}OK (1.1 equiv.), Bu^{t}OH, room temp., 1 h then $HC{\equiv}Cl^+PhBF_4^-$ (1.2 equiv.); ii, $PhN(C_2H_5)_2BI_3$(1 equiv.), AcOH, benzene, room temp., 14 h; iii, DIBAH (1.5 equiv.), toluene, −78 °C, 2 h; iv, see text



yield,[8] which was regiospecifically transformed into the alkenyl iodide **7** (90%) on exposure to BI_3-*N*,*N*-diethylaniline complex and acetic acid (20 °C, 14 h).[9] Diisobutylaluminium hydride (DIBAH) reduction of **7** in toluene at −78 °C gave the *cis*-diol **8** (71%) together with the *trans*-diol (9%). The stereochemistry of **8** was unequivocally determined from NOE experiments. With the aim of application to asymmetric synthesis, the reaction utilizing $Pd(OAc)_2$ and bis(diphenylphosphino)ethane (diphos) as a ligand was first investigated. After several attempts, it was found that treatment of **8** with $Pd(OAc)_2$ (5 mol%), diphos (10 mol%) and 3 mol equiv. of K_2CO_3 in dioxane under 1 atm of CO pressure (80 °C, 3 h) afforded the best result, giving **9** as a racemate in 78% yield. Use of other solvents such as dichloroethane and toluene gave **9** in 76 and 52% yields, respectively, while MeCN provided **9** only in 18% yield together with **10** (25%) and dimethyl sulphoxide (DMSO) gave **10** in 62% yield together with a small amount of **9**. These results suggest that decreasing solvent polarity favours carbonylation than elimination. Furthermore, use of K_2CO_3 as a base was found to be essential for the above process to be catalytic.



Scheme 3 *Reagents and conditions*: i, ethylene glycol (1.6 equiv.), TsOH(cat.), benzene, reflux, 1 h; ii, LDA (1.6 equiv.), THF, 4 °C, 15 min then $CH_2{=}N^+Me_2I^-$ (3.1 equiv.), −74 °C → room temp., 2 h; iii, MeI (excess), MeOH, room temp., 13 h; iv, aq. $NaHCO_3$, CH_2Cl_2, room temp., 2 h; v, $FeCl_3{\cdot}SiO_2$, acetone, room temp., 3 days

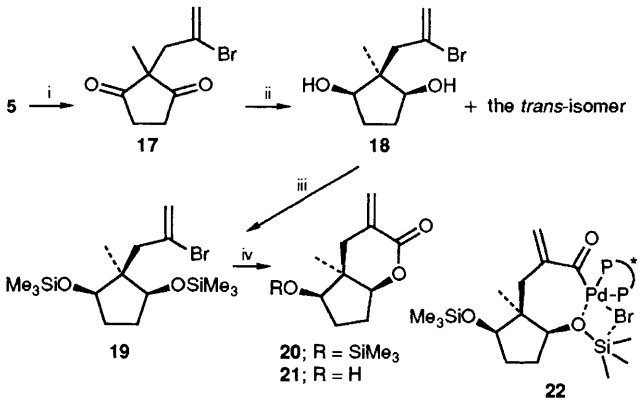
Table 1 Catalytic asymmetric synthesis of **9** and **13** from **8**[a]

				9		13	
Entry	Catalyst[b]	Base	Time/h	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)
1	**a**	Ag_2CO_3	43	19	34	8	27
2	**a**	Ag_2O	18	44	57	5	42
3	**a**	$TlNO_3$	14	79	22	14	6
4	**b**	TlOAc	12	74	50	17	39

[a] All reactions were carried out in MeCN under 1 atm of CO pressure (70 °C). [b] **a**: $Pd(OAc)_2$ (5 mol%), (*R*)-binap (10 mol%), **b**: Cl_2Pd(*R*)-binap (5 mol%).

Having established an efficient synthesis of **9** starting with the prochiral alkenyl iodide **8**, we next turned our attention to a catalytic asymmetric synthesis utilizing **8**, $Pd(OAc)_2$ and an optically active bidentate ligand in the presence of K_2CO_3. However, no asymmetric induction was observed in all the cases using optically active phosphorus ligands such as (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane [(*S*,*S*)-chiraphos], 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl [(*R*)-binap], *N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine [(*S*,*R*)-bppfa] and 1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine [(*S*,*S*)-bppm]. These results appeared to suggest that partial dissociation of a bidentate ligand occurred at the stage of hydroxy group coordination to Pd to keep the 16-electron configuration **11**,[10] thus giving racemic **9**. In order to avoid partial dissociation of a bidentate ligand, the reaction was then carried out in the presence of either a silver[6] or thallium salt.[11] These salts are believed to be effective in producing the Pd^+ intermediate **12**. Treatment of **8** with $Pd(OAc)_2$ (5 mol%), (*R*)-binap (10 mol%) and 3 mol equiv. of Ag_2O under 1 atm of CO pressure in MeCN (70 °C, 18 h) afforded **9** of 57% e.e. in 44% yield together with **13** of 42% e.e. (5%). Furthermore, exposure of **8** to Cl_2Pd(*R*)-binap (5 mol%) and 3 equiv. of TlOAc under 1 atm of CO pressure in MeCN (70 °C, 12 h) provided **9** of 50% e.e. in 74% yield and **13** of 39% e.e. (17%). The representative results are shown in Table 1. Other optically active bidentate ligands such as (*S*,*R*)-bppfa, (*S*,*S*)-bppm, (*S*,*S*)-chiraphos and 2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene [(+)-norphos] gave less satisfactory results. The e.e.s of **9** and **13** were calculated by HPLC analysis (Daicel, Chiralcel AS, hexane : propan-2-ol, 9 : 1), and the absolute configuration of **13** derived from **9** (PCC) was found to be the same as that of **13** (HPLC). The absolute configuration of **13** was determined by converting known **14**[12] to **13** (*via* **15** and **16**) as shown in Scheme 3. The mechanism of formation of **9** with Ag_2O afforded none of the corresponding ketone. Therefore, it is now supposed that some palladium species plays a key role in oxidizing **9**,[13] thus giving **13** of different e.e.

Encouraged by the results described above, we then turned our attention to a catalytic asymmetric synthesis of the α-methylene lactone **21**. The requisite prochiral alkenyl



Scheme 4 *Reagents and conditions*: i, 2,3-dibromopropene (1.4 equiv.), aq. Bu_4NOH (1 equiv.), THF, room temp, 12 h; ii, DIBAH (1.5 equiv.), toluene, −78 °C, 2 h; iii, trimethylsilyl chloride (1.7 equiv.), NEt_3 (3.1 equiv), 4-dimethylaminopyridine (cat.), CH_2Cl_2, room temp., 8 h; iv, $Pd(OAc)_2$ (5 mol%), (*S,S*)-chriaphos (10 mol%), K_2CO_3 (1 mol equiv.), CO (1 atm), DMSO, 80 °C, 1 h

bromide **18** was efficiently synthesized *via* **17** as shown in Scheme 4. Although many experiments were carried out to obtain **21** in an optically active form, asymmetric induction was not observed in any case. Although racemization of **9** was not observed in the reaction medium, we noticed that complete racemization of **21** occurred in the reaction medium due to the presence of a lactone moiety in very close proximity to a hydroxy group. For this reason, the catalytic asymmetric synthesis starting with the disilyl ether **19** was next attempted. It was found that treatment of **19** with $Pd(OAc)_2$ (5 mol%), (*S,S*)-chiraphos (10 mol%) and 1 mol equiv. of K_2CO_3 under 1 atm of CO pressure in DMSO (80 °C, 1 h) afforded the best result, giving **20** of 39% e.e. (41%) together with racemic **21** (24%). Determination of the absolute configuration of **20** has not been achieved because of the fact that **21** is readily racemized. To the best of our knowledge, this is the first example of the α-methylene lactone formation starting from an alkenyl halide possessing an internal silyl ether.[14] The reaction appears to proceed through **22**.

In conclusion, we have developed a catalytic asymmetric synthesis of the α-methylene lactones **9**, **13** and **20** in up to 57% e.e. starting with the prochiral alkenyl halides **8** and **19**. Although the enantiomeric excess is at best modest, the results described in this paper provide mechanistic information concerning a catalytic asymmetric carbonylation starting with an alkenyl halide, and also pave the way for further improvements. Further studies along this line are in progress.

This work was financially supported by Grant-in-Aid for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture, Japan. The authors acknowledge Professor M. Ochiai of Gifu Pharmaceutical University for valuable comments on the preparation of ethynyl(phenyl)iodonium tetrafluoroborate.

Received, 15th July 1991; Com. 1/03597E

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